be obvious to modify this medium with EDTA and pH buffer. Applicants respectfully disagree with this rejection.

As an initial matter, applicants contend that the technical field of the Dunphy reference implicitly limits histological procedures to only tissue preservation for mortuary science and pathologic evaluation. Specifically, Dunphy states: "The present invention relates to the field of preservation of human tissue in the mortuary science and the anatomic pathology (histology) disciplines." (column 1, lines 7-9). Also, Example 4 (which is cited by the Examiner) specifically states that the medium described is for "histological study and evaluation." (column 7, lines 62-63). To one skilled in the art of "histology", procedures in the histology field are interpreted as microscopic procedures, not molecular. For example, the definition of histology from the Encarta World Dictionary (Encarta® World English Dictionary [North American Edition] © & (P) 2001 Microsoft Corporation), states: "**histology** *noun* **microscopic tissue study:** a branch of anatomy concerned with the study of the microscopic structures of animal and plant tissue. **histologic** *adjective*, **histological** *adjective*, **histologically** *adverb*, **histologist** *noun*." Most revealing is the title of the Dunphy reference, " Formaldehyde-Free tissue Preservative Compositions". The emphasis on formaldehyde-free compositions implies that the scope of the Dunphy invention does not encompass molecular applications that could benefit from formaldehyde-containing media.

From a practical point of view, the fields of histology and molecular biology are worlds apart. For histology, harsh fixation is acceptable as it is sufficient to preserve the tissue morphologically and to then cut the tissues and stain them with simple dyes that can permeate the tissues so they can be physically viewed. It is a completely different matter to use the tissues or cells for molecular testing. In that case, very gentle and different fixation is required so that

the molecules in the tissue can be retained intact and useable for the molecular tests. Thus, one skilled in the art would not look to the Dunphy reference for a medium useful for molecular biological analysis.

The Examiner states that it is obvious to a person of ordinary skill to modify the tissue collection medium of Dunphy in Example 4 by addition of buffer and EDTA, "because Dunphy shows that EDTA has a bacteriostatic effect that is desirable in a tissue fixation medium." Applicants respectfully disagree.

Regarding addition of EDTA to the Dunphy formulation of Example 4, applicants respectfully disagree with the Examiner's characterization of the Dunphy reference. The Examiner cites col. 5, lns. 1-7 for the description "that a chelating agent EDTA is a useful addition because it acts as a bacteriostatic agent." This description is cited completely out of context. Column 5, lns. 1-7 is part of a section in Dunphy describing an *arterial injection fluid.* Reading the Dunphy reference, it is clear that the reference is divided into the description of four different formulations: (1) a "Pre-Injection (and Co-Injection) Fluid" (col. 2, ln. 51 – col. 3, ln. 52); (2) an "Arterial Injection (Tissue preservative) Fluid" (col. 3, ln. 53 – col. 5, ln. 12); (3) a "Body Cavity Fluid" (col. 5, ln. 13 – col. 6, ln. 7); and (4) a "Formaldehyde-Free Tissue Fixation Fluid" (col. 6, lns. 8–60). The four Examples which follow these descriptions correspond to the four formulations, so that Example 1 embodies a pre-injection fluid, Example 2 is an arterial injection fluid ("injectable tissue preservative composition"), Example 3 is a body cavity fluid, and Example 4 is a formaldehyde-free tissue fixation fluid.

The Examiner has improperly mixed and matched the various different formulations to reach the claimed invention. In doing so, the Examiner raises the issue of how one skilled in the art should recognize that all of the ingredients of one Example should be mixed

with just one of the ingredients of another Example. How could the skilled artisan know which ingredients and at what concentration to select, from all of the various ingredients and concentrations and various pH values, to correctly reach the claimed invention? There is no basis in Dunphy that would lead the skilled artisan to a reasonable expectation of success of recognizing that EDTA can be added to a formaldehyde-free tissue fixation fluid of Example 4 for the purpose of nucleic acid preservation, when Dunphy himself does not add EDTA to this formulation. Applicants assert this correct conclusion could only be reached by applying hindsight. And this is improper.

Dunphy specifically omits EDTA in the formulation of Example 4. Its absence is quite conspicuous because EDTA is included in Examples 1 and 2. Dunphy, by omitting EDTA in Example 4 is providing the specific teaching that although EDTA may be useful in formulations for a preinjection fluid and an arterial injection fluid, it is NOT recommended in the formaldehyde-free tissue fixation fluid, exemplified in Example 4. Thus, the addition of EDTA, or any anti-degradation agent to the Dunphy formulation of Example 4 would not be obvious to one of skill in the art.

In sum, the molecular biologist would not look to the Dunphy reference because it is concerned with mortuary-type preserving solutions (i.e. not nucleic acid preservation). The artisan would also understand Dunphy as teaching that EDTA is NOT to be added to the formaldehyde-free tissue preservation fluid of Example 4, as compared to some of the other formulations described by Dunphy. Finally, because molecular biological analysis of the tissue samples is not contemplated by Dunphy, NO anti-degradation agents are described for the formaldehyde-free tissue preservation fluid. So, one skilled in the art would not be motivated to add such an ingredient to this composition. In fact, the skilled artisan would consider Dunphy as

teaching away from the addition of EDTA to the formulation of Example 4. For these reasons, applicants respectfully request reconsideration and withdrawal of the §103 rejection.

2. Claims 49, 55-57, 60, and 68-74 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Dunphy, U.S. Patent No. 5,679,333, in view of Weber, International Publication No. WO 94/02645, further in view of Harrison, U.S. Patent No. 4,578,282. The Examiner contends that Dunphy as applied to Weber and Harrison makes it obvious to use tissue sample treated with the medium of Dunphy for methods of DNA and protein analysis, as Weber shows that such media can be used for DNA hybridization studies and Harrison shows that such media may be used for antigen analysis. Applicants respectfully disagree with this rejection.

First of all, combining Dunphy with Weber and Harrison is improper as these references originate from fundamentally different areas of art. One skilled in the art of molecular biology would not look to Dunphy for a media to preserve a tissue sample for nucleic acid or protein analysis. Weber is concerned with *in situ* hybridization techniques of genes from *previously stained* tissue samples. And Harrison is concerned with a dry reagent for antigen detection on slides. All three of these references are from divergent areas of science and would not identified by the skilled artisan in a search for a medium having both cytological and molecular biological capabilities.

The combination of cited references simply would not lead the skilled artisan to the claimed invention. As an initial matter, the entire focus of the Dunphy reference is based upon the fact that the formulations described are all "formaldehyde-free". Specifically, Dunphy states: "All of the solutions share the common attribute of not containing formaldehyde in their

composition". (Dunphy, col. 2, lns 1-2). Compare this to Weber, who suggests use of both alcohols and aldehydes. Compare this teaching to Harrison, which describes a dry fixing agent. Harrison specifically states "[The Harrison invention] is to be contrasted with previous fixative compositions utilizing such materials as formaldehyde and alcohols." "Rather the mixture appears to 'tie up' water molecules within the cell or material, maintaining both cellular and immunological characteristics." (Harrison, col. 2, lns 35-40). Therefore, these three references describe a wide variety of fixing agents, used at a variety of concentrations.

The Examiner cites the Weber and Harrison references as descriptions of the particular molecules being analyzed and relies primarily on Dunphy for a teaching of the formulation and method of use. However, applicants urge this type of analysis ignores the whole teachings of the various references. As the Examiner well knows, §103 requires a showing of obvious of the invention "as a whole". To evaluate obviousness, a comparison must be made between the prior art as a whole and the claimed subject matter as a whole. *In re Lange and Haynes*, 465 F.2d 896 (CCPA 1972). Viewed another way, obviousness is measured by considering whether a hypothetical person having all the art at hand would have found the same solution when addressing himself to the same problem. *Stratoflex, Inc. v. Aeroquip Corp.*, 561 F.Supp. 618 (Mich. 1982). Applicants assert that Dunphy, Weber and Harrison, when combined and properly viewed "as a whole", do not lead the skilled artisan to recognize the claimed invention.

In particular, when the cited references are viewed "as a whole" and in the combination cited by the Examiner, it becomes clear that the skilled artisan could not reach the presently claimed invention. As discussed above, in Dunphy Example 4 the use of ethanedial at 3.5-4% concentration is described, but the formulation fails to describes an anti-degradation

agent (i.e. the "formaldehyde-free tissue preservation fluid). Weber describes the use of alcohols and aldehydes as fixatives, but also fails to teach or suggest any anti-degradation agent. In fact, Weber uses proteinase K and guanidine isothiocyanate (*see* Weber at pages 20 and 25). These reagents are potent degradation agents of proteins and would be undesirable in the claimed medium for detection of proteins. Harrison, on the other hand, is concerned with detection of proteins, but not with nucleic acids. In particular, Harrison describes a dry fixative reagent, which "comprises as its principal fixative and preservative component a four component mixture of pyrrolid-2-one, a polyol, at least one urea and a zinc salt of a non-oxidizing organic or inorganic acid" (Harrison, col. 2, lns 7-10). Harrison also states, as the Examiner has pointed out that "glutaraldehyde" can be used as an additional fixative. None of the Harrison reagents are part of the Dunphy or the Weber solutions. How would the skilled artisan know which of these ingredients to choose? And what would motivate the skilled artisan to reject most of the components of Harrison (except glutaraldehyde), which detect proteins, and most of the components of Weber (except formaldehyde), which detect nucleic acids and select the components of Dunphy, a mortuary-type tissue preservation solution?? And how would the skilled artisan recognize to add EDTA to this formulation? Applicants assert that the components and steps of the claimed methods can be reached reading these references ONLY by the improper use of hindsight. The invention as a whole is not obvious to the skilled artisan, in view of Dunphy, Weber and Harrison (individually or when combined), when these references are taken as a whole.

Further the addition of EDTA or any anti-degradation agent is not taught or suggested in the Dunphy reference in their discussion of Example 4, cited by the Examiner. Weber does not remedy this defect, in that it too does not teach or suggest the addition of EDTA

or any anti-degradation agent. Harrison, similarly, does not remedy the defect of the Dunphy and Weber references, in that it too does not teach or suggest the use of EDTA or any anti-degradation agent.

Applicants also wish to point out that the Examiner's combination of Dunphy's "formaldehyde-free tissue preservation fluid" of Example 4 with Weber's mention of the use of formaldehyde is puzzling. With Dunphy as the primary reference, and hence the primary teaching, the skilled artisan would conclude that formaldehyde is to be avoided (hence, the title of the Examiner-selected formulation). If the skilled artisan were truly interested in measuring nucleic acids, then the artisan would not rely on Dunphy's formulation. The two reference directly contradict each other as to the use of formaldehyde. Thus, the skilled artisan, reading Dunphy and Weber would at best be confused.

For the above reasons, applicants assert that the claimed invention is not obvious in view of Dunphy, Weber and Harrison. Applicants respectfully request reconsideration and withdrawal of the §103 rejection.

Additionally, as relates to the method claims, neither Dunphy nor Weber nor Harrison meet the limitations of these claims, in that claims 55-57 and 68-74 recite specific and separate steps for cell morphology analysis and RNA, DNA or protein analysis. Neither Dunphy, nor Weber nor Harrison teach or suggest a method for carrying out both types of analysis with a single medium. Therefore, these claims are not obvious in view of the cited prior art. Applicants respectfully request reconsideration and withdrawal of the §103 rejection.

3. Claims 62-66 were rejected under 35 U.S.C. § 103(a) for being unpatentable over Dunphy U.S. Patent No. 5,679,333 in view of Wainwright U.S. Patent No. 5,370,128. The

Examiner contends that Wainwright discloses an article of manufacture comprising a container, a lid fitting the container and a brush for preserving a cell sample. Applicants respectfully disagree with this ground of rejection.

As discussed above Dunphy fails to make obvious the claimed invention, because it would not be obvious to one of skill in the art to add EDTA to the formulation of Example 4. The Examiner's citation of Dunphy for the teaching of the addition of EDTA is particular to one of two of the formulations described in Dunphy. A total of four formulations are described in Dunphy (*see* above discussion of Dunphy). In the two other formulations, the "formaldehyde-free tissue preservation fluid" and the "body cavity fluid", Dunphy specifically does not add EDTA and in the description of these two formulations, Dunphy does not describe the addition of EDTA. Therefore, one skilled in the art reading the Dunphy reference would specifically learn that only two of the formulations should contain EDTA, while the other two should NOT contain EDTA, one of which is the cited formulation. Therefore, Dunphy teaches away from using EDTA in the formaldehyde-free tissue preservation fluid of Example 4.

Wainwright does not remedy the defect of Dunphy, but rather merely describes a container with a lid and a brush. Wainwright only refers to a fixative once, "Inside the container is 2 CCs of cytofixative to preserve the specimen." (column 5, lines 43-44). Wainwright does not disclose what this cytofixative may be composed of, nor does Wainwright disclose that this cytofixative may enable the fixation of cells for molecular analysis.

Applicants assert that the claimed invention is not obvious in view of Dunphy and Wainwright. Neither of these references, taken alone or in combination teaches or suggests the articles of manufacture as claimed. Neither Dunphy nor Wainwright teaches or suggests all of the components of the claimed medium. Therefore, Dunphy in view of Wainwright does not

teach or suggest the kit claims of claim 62-66. Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

4. Claim 67 was rejected under 35 U.S.C. § 103(a) for being unpatentable over Dunphy, in view of Wainwright, further in view of Weber, in view of Harrison. The Examiner contends that this combination is warranted because Weber and Harrison respectively show that aldehydes, such as formaldehyde or glutaraldehyde, are useful cross-linking agents in tissue collection media. Applicants respectfully disagree with this rejection.

As discussed above, the inventions of Dunphy, Wainwright, Weber and Harrison each pertain to purposes (and thus compositions) that conflict with each other. Dunphy pertains to formaldehyde-free formulations and originates from the technical field of Dunphy of mortuary science. One skilled in the art would be confused as to whether to combine the formaldehyde-free formulations of Dunphy with the formaldehyde-containing formulations of Weber. Secondly, the combination of Weber and Harrison is improper because Weber discloses the use of proteolytic and denaturing agents (such as proteinase K and guanidine isothiocyanate) that would not enable the further analysis of proteins. Wainwright merely provides a container, a lid and a brush, and therefore, provides nothing to remedy the deficiencies of the references describing specific media. None of the cited references teaches or suggest the use of EDTA or any anti-degradation agent to reach the media of the present invention. Thus, applicants respectfully disagree with the combination of Dunphy, Wainwright, Weber and Harrison because these references, taken alone or in combination do not teach or suggest all the limitations of claim 67. Therefore, applicants respectfully request reconsideration and withdrawal of this ground of rejection.

As relates to the Declaration of Dr. Lorincz, applicants submit herewith a stamped return postcard indicating receipt by the United States Patent and Trademark Office of the Declaration. Thus, applicants do not understand the Examiner's statement "nor was such a declaration attached to the amendment received 31 July 2001." As a courtesy, applicants provide herewith a copy of the filed Declaration for the Examiner's consideration.

Response to Double Patenting Rejection

Claims 36-74 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 29-41, 46-55, 60-66, 71-75, and 80 of copending application Serial No. 09/598,571, in view of Weber, in view of Harrison. Applicants respectfully disagree with the combination of the co-pending application with Weber and Harrison.

Applicants respectfully traverse this rejection as premature because co-pending application Serial No. 09/598, 571 has not yet been allowed. Applicants provisionally agree to file a terminal disclaimer upon issuance of claims in this application. The filing of a terminal disclaimer to obviate a rejection based on non-statutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991). Applicants respectfully request reconsideration and withdrawal of the double patenting rejection.

AUTHORIZATION

No additional fee is believed necessary.

However, the Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No.

13-4500, Order No. 2629-4005US1.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition and for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 2629-4005US1. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,

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Dated: Jan. 18, 2002

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